REVIEW ARTICLE

Uveitis in Juvenile Idiopathic Arthritis

Arnd Heiligenhaus, Kirsten Minden, Dirk Föll, Uwe Pleyer

SUMMARY

Background: Juvenile idiopathic arthritis (JIA) is the most common systemic disease causing uveitis in childhood, with a prevalence of 10 per 100 000 persons. JIA often takes a severe inflammatory course, and its complications often endanger vision.

Methods: This review is based on pertinent articles retrieved by a selective literature search up to 18 August 2014 and on the current interdisciplinary S2k guideline on the diagnostic evaluation and anti-inflammatory treatment of juvenile idiopathic uveitis.

Results: Uveitis arises in roughly 1 in 10 patients with JIA. Regular eye check-ups should be performed starting as soon as JIA is diagnosed. 75–80% of patients are girls; antinuclear antibodies are found in 70–90%. The risk to vision is higher if JIA begins in the preschool years. As for treatment, only a single, small-scale randomized controlled trial (RCT) and a small number of prospective trials have been published to date. Topical corticosteroids should be given as the initial treatment. Systemic immunosuppression is needed if irritation persists despite topical corticosteroids, if new complications arise, or if the topical steroids have to be given in excessively high doses or have unacceptable side effects. If the therapeutic effect remains inadequate, conventional and biological immune modulators can be given as add-on (escalation) therapy. Treatment lowers the risk of uveitis and its complications and thereby improves the prognosis for good visual function.

Conclusion: Severely affected patients should be treated in competence centers to optimize their long-term outcome. Multidisciplinary, individualized treatment is needed because of the chronic course of active inflammation and the ensuing high risk of complications that can endanger vision. Future improvements in therapy will be aided by prospective, population-based registries and by basic research on biomarkers for the prediction of disease onset, prognosis, tissue damage, and therapeutic response.

► **Cite this as:**

Heiligenhaus A, Minden K, Föll D, Pleyer U: Uveitis in juvenile idiopathic arthritis. *Dtsch Arztebl Int* 2015; 112: 92–100. DOI: 10.3238/arztebl.2015.0092

The term “uveitis” describes inflammations of different etiologies that affect the inner layers of the eye. Intraocular inflammations are rarer in children than in adults. Their prevalence in children and adolescents up to the 16th year of life in Europe is estimated to be 25–30/100 000 (1–3, e1), which means that the disease complex has the status of an orphan disease. The disease spectrum in children includes infections as well as uveitis in inflammatory rheumatic disorder and uveitis masquerade syndromes (*Box 1, Table 1, Box 2*). Careful etiologic investigation is therefore required. This is based on the anatomical form of the uveitis, the medical history, and the suspected clinical diagnosis (see the interdisciplinary S2k guideline on the diagnostic evaluation and anti-inflammatory treatment of juvenile idiopathic uveitis, Association of the Scientific Medical Societies in Germany [AWMF] register No 045/012) (e2, e3).

The most common disorder underlying uveitis in children is juvenile idiopathic arthritis (JIA) (1, 3, 4). JIA-associated uveitis is estimated to have a poor prognosis and has a high rate of complications (2, 3, 5). It is associated with far-reaching consequences for patients and substantial socioeconomic burdens (2, 6, 7, e4). Early diagnosis and rapid adequate interdisciplinary care are of crucial importance for the long-term prognosis. In contrast to intraocular inflammation in adults, patients with JIA-associated uveitis rarely express complaints and externally no irritations are visible (2, 3, 5). For this reasons, a high index of suspicion is indicated in all medical areas.

This article is based on a detailed literature search, meta-analyses, and current guidelines. Readers will be informed about diagnostic and therapeutic standards relating to JIA-associated uveitis as well as gain perspectives for future patient care.

Epidemiology

With a prevalence of 0.1%, JIA is the most common inflammatory rheumatic disorder in childhood and adolescence (8, e5). The term describes a group of chronic joint disorders of unknown cause, which occur before the 16th year of life and last for a minimum of 6 weeks (4). According to the current classification of the International League of Associations for Rheumatology (ILAR) (4), seven subgroups are distinguished in the first 6 months of onset, on the basis of clinical characteristics (for example, the number of affected joints, extra-articular manifestations, the presence of rheumatoid factors).

Department of Ophthalmology, St. Franziskus Hospital, Uveitis Center, University of Duisburg-Essen: Prof. Dr. med. Heiligenhaus

German Rheumatism Research Centre Berlin (DRFZ), University Medicine, Berlin: PD Dr. med. Minden

Department of Pediatric Rheumatology and Immunology, University Children's Hospital Münster: Prof. Dr. med. Föll

Department of Ophthalmology, Charité – Universitätsmedizin Berlin: Prof. Dr. med. Pleyer

Data on the rates of uveitis in JIA (4–24%) vary substantially because of the characteristics of different medical centers and geographical variations (3, 5). The risk of uveitis is higher in north Europeans than in persons of Asian origin (3). According to a meta-analysis, the estimate worldwide incidence is 8.3% (5). A recent multicenter data collection in Canada determined a rate of newly occurring uveitis manifestations after a diagnosis of JIA of 2.9% per year for the first three years after disease onset (e6). In Germany, one in 10 patients will develop uveitis within their first four years after onset of JIA (3, 9).

According to all analyses, the JIA subtype crucially affects the rates of uveitis (3, 5). According to the nationwide “Kerndokumentation rheumakranker Kinder und Jugendlicher” [the central registry of children and adolescents with rheumatic disorders], three quarters of JIA patients with uveitis have oligoarthritis (*Table 2*). By contrast, systemic juvenile idiopathic arthritis or rheumatoid factor–positive polyarthritis are rarely (<1%) accompanied by uveitis (3, 5, 9, 10).

The intraocular inflammation is mostly diagnosed between the 4th and 6th years of life (2, 5, 9, 10). In half of patients, the uveitis manifests shortly before or within four to five months after arthritis onset, in some 75% within a year, in 90% within four years, and in only 3–5% before or five or more years after the onset of JIA (9, 10).

In 75% of children the inflammation affects both eyes, simultaneously or within a few months of each other. Children with initially unilateral uveitis very rarely develop uveitis in the contralateral eye once more than 12 months have passed (8, 11).

Risk factors for manifestation

Age at arthritis onset

In patients with early-onset arthritis, the risk of uveitis is strikingly increased. The mean age at initial manifestation of JIA is between six and seven years, whereas children who additionally develop uveitis develop JIA earlier: in the fourth and fifth years of life (9–11).

Sex

JIA-associated uveitis is more commonly observed in girls (75–80%). Since this observation is the same for the total cohort of JIA patients with uveitis, this is not considered an independent risk factor (5, 9, 10).

Antinuclear antibodies

Antinuclear antibodies (ANA) are seen more often in JIA with uveitis (70–90%) than in JIA without uveitis (30–42%) (9, 10). The cumulative incidence of uveitis is significantly higher in ANA-positive patients than in ANA-negative patients (5). The level of the ANA titer does, however, not correlate with the risk of developing uveitis or with the severity of uveitis (5, 9).

Genetic factors

Several genetic markers are associated with the more common occurrence of uveitis in JIA. Recent indi-

BOX 1

Causes of infectious uveitis in childhood and adolescence

- **Anterior uveitis**
  - Herpes simplex virus
  - Varicella zoster virus
  - Cytomegalovirus
  - Tuberculosis
  - Borreliosis
  - Syphilis
- **Intermediate uveitis**
  - Tuberculosis
  - Borreliosis
- **Posterior uveitis**
  - Herpes simplex virus
  - Varicella zoster virus
  - Toxoplasmosis
  - Toxocariasis
  - Human immunodeficiency virus (HIV)
  - Syphilis

cations have highlighted the role of HLA-DRB1*11 and *13 locus (odds ratio 3.4) (e7, e8). Interestingly, the different risk factors seem to be of different relevance in ethnically different populations (e9).

Clinical presentation

According to the classification of the international Standardization of Uveitis Nomenclature (SUN) (12), which seeks to classify intraocular disorders, JIA is typically accompanied by recurrent, non-granulomatous, anterior uveitis. The inflammation affects primarily the anterior eye segment; the secondary result is a disruption of the blood-aqueous and blood-retinal barrier.

Characteristically, the onset of uveitis and subsequent episodes remain unnoticed by the affected children and their parents in more than 85% of cases (5, 9, 10). It should be borne in mind that JIA-associated uveitis is most common in the early-childhood forms of JIA and that these very young patients do not often report symptoms even if their visual acuity loss is advanced. This form of uveitis therefore entails a higher risk of delayed diagnosis than acute uveitis (e10), which is typically seen in enthesitis-related arthritis (5, 9, 10). Even severe intraocular inflammation usually remains asymptomatic, without any externally visible irritations, and can be detected only by an ophthalmologist using a slit lamp. In order to detect uveitis as early as possible, all patients in whom JIA is acutely suspected or in whom the diagnosis of JIA has been confirmed need to be examined by an ophthalmologist.

TABLE 1

Important immune-mediated uveitis-associated disease entities in childhood and adolescence (cited from the interdisciplinary S2k guideline on the diagnostic evaluation and anti-inflammatory treatment of juvenile idiopathic uveitis (JIA); AWMF registry No 045/012).

Disease entity	Rate of uveitis and clinical presentation	Supportive laboratory markers	Clinical symptoms affecting the eye
1 JIA			
1.1 RF-negative polyarthritis	5–10%, often bilateral	ANA (30%)	Asymptomatic
1.2 RF-positive polyarthritis	Very rare	IgM-RF	
1.3 Systemic arthritis	Very rare	Ø	
1.4 Oligoarthritis	Onset in early childhood: 10–40%, often bilateral	Onset in early childhood: ANA 70–90%	Onset in early childhood: asymptomatic
Persistent oligoarthritis	10–20%		
Extended oligoarthritis	20–40%		
1.5 Psoriatic arthritis	a) Onset in early childhood: up to 20%, often bilateral b) onset at school age: 10%	a) ANA 60–70% b) ANA 10%	a) Asymptomatic b) Asymptomatic or symptomatic
1.6 Enthesitis-related arthritis	20%, acute episodes affecting both eyes in turn	HLA-B27	Symptomatic
2 Juvenile ankylosing spondylitis	20–25%, Acute episodes affecting both eyes in turn	HLA-B27	Symptomatic
3 Reactive arthritis		HLA-B27	Symptomatic
4 Inflammatory bowel disease	up to 10–15%, acute episodes affecting both eyes in turn	HLA-B27	Asymptomatic or symptomatic
5 Sarcoidosis 5a Blau syndrome	60–70% (infantile sarcoidosis), often bilateral, Blau syndrome familial	Mutation in the NOD2 gene	Asymptomatic
6 Behçet's disease	10–50%, often bilateral	HLA-B51 (40–60%)	a) Anterior uveitis, panuveitis symptomatic b) Posterior uveitis asymptomatic
7 Systemic vasculitides, collagenoses	Unclear	ANCA, ANA, dsDNA antibodies	Symptomatic or asymptomatic
8 Lyme arthritis	Unclear	Serology, Western blot	a) Anterior uveitis: symptomatic b) Posterior uveitis: asymptomatic
9 CINCA/NOMID	40–60%, often bilateral	Mutation in the NLRP3 gene	a) Anterior uveitis: asymptomatic or symptomatic b) Intermediate/posterior uveitis: asymptomatic

ANA, antinuclear antibodies; HLA, human leukocyte antigen; RF, rheumatoid factor; ANCA, anti-neutrophil cytoplasmic antibodies; CINCA, chronic infantile neurologic cutaneous and articular; NOMID, neonatal onset multisystem inflammatory disease

Complications

Adherences between iris and lens (posterior synechiae) develop in cases of high inflammatory activity as a result of fibrin exudation. They are a common complication and accelerate opacification of the lens (cataract) (11, 13) (*Figure 1*). Cataract formation as the most common complication impairing visual acuity (19–81%) is furthermore advanced by chronic inflammation and intensive topical and/or systemic corticosteroid treatment (5). Additionally, ocular hypertension (≥ 22 mm Hg) and secondary glaucoma—with optic nerve damage and visual field defect—are typical and common complications (10–40%) (14, 15). New, non-invasive procedures for retinal examination (so-called

optical coherence tomography) can detect inflammatory macular edema far earlier than had been assumed previously (16, e11). Severe inflammation in the ciliary body may be followed by inflammatory infiltration of the vitreous, affecting visual acuity, ocular hypotension, and shrinking of the eye (phthisis bulbi). If clouding of the optical media develops at a pre-school age there is a risk of amblyopia.

20–45% of patients have complications even at their initial diagnosis of uveitis (9, 10). Two or three decades ago, the reported complication rates in a chronic inflammatory course were 60–90% after 6–10 years (17, e12, e13). The frequency of complications and the rate of vision loss have been noticeably lowered in recent

years (5, 18, 19). In spite of this, JIA-associated uveitis is still associated with a high risk of late sequelae and a great risk for loss of visual acuity (13, 20).

The most important predictors of a complicated course of uveitis and loss of visual acuity have been found to be synechiae, a high degree of inflammation (number of cells in the anterior chamber >2+) (12), dense infiltration of the vitreous body, cataract, glaucoma, and macular edema (2, 9, 11, 13). Further indicators of a poor prognosis for a patient's vision include uveitis manifestation at an early age and a short interval between the manifestations of arthritis and uveitis. The prognosis is particularly poor if uveitis develops before the arthritis (11, 13, 20–22, e14, e15).

The risk of complications endangering visual acuity is lower in JIA patients with symptomatic uveitis (<15% of cases, 40% HLA-B27 positive) (e10). Such children have enthesitis-related arthritis in most cases, which manifests at an older school age and affects primarily boys (e10). Typically, this form of arthritis is accompanied by unilateral acute anterior uveitis with an episodic course (e10). The main symptoms include a painful red eye, photophobia, and visual impairment. The prognosis is mostly good because patients present to the ophthalmologist and treatment is given at an early stage (23).

Diagnostic evaluation

Table 3 summarizes the currently recommended intervals for uveitis screening that are adapted to the uveitis risk of the individual JIA categories. Screening aims to detect uveitis before irreversible sequelae can develop. Routine examinations with medical history, visual acuity, slit lamp, tonometry, and funduscopy can be undertaken in any ophthalmological practice. Where complications are clinically suspected, additional investigations are required that are based on the individual findings (see AWMF registry No 045/012).

Anti-inflammatory treatment

According to our current understanding, JIA-associated uveitis is a multifactorial autoimmune disorder with disrupted innate and adaptive immune reactions in persons with a genetic predisposition (e16). Its etiopathogenesis is not yet fully understood. Current unspecific anti-inflammatory treatments are based on the activity of the uveitis, complications, and the risk of irreversible vision loss (IIIA). Such therapies aim to save the patient's vision, treat the acute episode as well as complications if any, and avoid recurrences and sequelae as well as adverse medication effects (IIIA). The treatment has to be tailored to the individual patient. The course of the underlying inflammatory rheumatic disorder needs to be considered. Children with JIA and uveitis who have predictors for a risk of visual acuity loss should be placed under the joint care of an ophthalmologist with special experience with the disease entity (uveitis center) and a pediatric rheumatologist.

So far, only a small randomized controlled trial and few prospective comparative studies of the treatment of children with uveitis in JIA have been conducted. For

BOX 2

Differential diagnoses (uveitis masquerade syndromes) (e3)

- **Malignant disorders**
  - Retinoblastoma
  - Leukemic infiltrate
  - Medulloepithelioma
- **Non-malignant disorders**
  - Coats' disease
  - Juvenile xanthogranuloma
  - Persistent hyperplastic primary vitreous
  - Retinal detachment
  - Astrocytoma
  - Cavernous retinal hemangioma
  - Retinopathy of prematurity
  - Norrie disease
  - Incontinentia pigmenti
  - Retinal choroidal coloboma

TABLE 2

Cumulative incidence of uveitis in the individual subgroups of juvenile idiopathic arthritis (JIA)*

JIA subgroups	Patients with uveitis	Risk of uveitis (univariate analysis)	
	n (%)	OR	95% CI
Systemic arthritis	4 (2.0)	1.0	
Persistent oligoarthritis	289 (13.5)	7.7	2.8–20.9
Extended oligoarthritis	92 (19.1)	11.7	4.2–32.2
RF-negative polyarthritis	59 (6.5)	3.4	1.2–9.5
RF-positive polyarthritis	3 (2.2)	1.1	0.2–5.0
Psoriatic arthritis	15 (4.5)	2.3	0.8–7.2
Enthesitis-related arthritis	31 (6.2)	3.3	1.1–9.3
Other JIA	15 (8.2)	4.4	1.4–13.6

* Data source: nationwide "Kerndokumentation rheumatischer Kinder und Jugendlicher" (the central registry of children and adolescents with rheumatic disorders) for 2012, German Rheumatism Research Center Berlin, 61 documenting institutions [e28]
CI, confidence interval; OR, odds ratio; RF, rheumatoid factor

Figure 1: Split lamp finding in a 6 year old girl with JIA-associated uveitis. Posterior synechiae and cataract. Typically, no external irritation is visible

this reason, the current treatment recommendations are based primarily on a consensus in the German-language guideline process (AWMF registry No 045/012) (24). (Evidence levels I–III and recommendation grades A, B, 0; see *eTables 1 and 2*).

Active uveitis has to be treated (IA). Topical steroids should be used as first-line treatment (IA). Non-steroidal anti-inflammatory drugs (NSAIDs) should not be used as monotherapy in active uveitis (IB). Systemic immunosuppression is required if using topical steroids does not result in uveitis inactivity within three months, if new complications arise, if the dosage of the corticosteroids has to be excessively high, or if medication-related adverse effects develop (IIIA) (*Figure 2*) (24). In patients with particularly severe inflammation, the treatment can be intensified at an earlier stage (IIIA). Immunomodulating and disease-modifying substances

(DMARDs, disease modifying antirheumatic drugs) often do not only make it possible to use lower dosages of corticosteroids but also improve the long-term course of uveitis (IIIA) (19). The current DMARD of choice is methotrexate (IIIA) (e17, e18). If after four months the effect is unsatisfactory, a second conventional or biological DMARD should be used (IIA). Currently, the preferred drug in this setting is the TNF-alpha-inhibitor adalimumab (IIA) (25, 26, e19, e20). The only RCT conducted thus far did not find any good evidence for the effectiveness of the DMARD etanercept, which is the biological response modifier most commonly used in JIA (e21).

In cases of therapeutic failure, other non-biological (azathioprine IIIB, mycophenolate mofetil III0, leflunomide III0) or biological DMARDs (abatacept III0, tocilizumab IIIB, rituximab IIIB) are used (27–29). None of the listed DMARDs is explicitly licensed for the treatment of JIA-associated uveitis, but methotrexate, adalimumab, abatacept, and tocilizumab are licensed for the treatment of polyarticular JIA. Ciclosporin A is of low effectiveness in JIA-associated uveitis and should not be used as the primary immunosuppressant (IIIA) (e22). Experts consider intravitreal surgical delivery of corticosteroids as nothing more than a rescue procedure (IIIA).

Monitoring of disease course and inflammatory activity

In patients with known uveitis, the intervals between control examinations by an ophthalmologist are based on the individual disease course. Patients with severe inflammation and certain complications (for example, glaucoma) may have to have daily check-ups at certain times (24). Important parameters for assessing the

TABLE 3

Ophthalmological screening intervals in patients with juvenile idiopathic arthritis (JIA)*

JIA subgroup	ANA	Age at JIA onset (in years)	JIA duration (in years)	Recommended screening intervals (in months)
OA, RF-PA, PsA, AO	+	≤ 6	≤ 4	3
			> 4	6
			≥ 7	12
	–	> 6	≤ 2	6
			> 2	12
			≥ 4	12
ERA	N/A	N/A	N/A	12
RF+ PA, Sys A	N/A	N/A	N/A	12
Patients with uveitis	N/A	N/A	N/A	According to disease course

*The control intervals relate to children without prior manifestation of uveitis (9).
ANA, antinuclear antibodies; Sys A, systemic arthritis; OA, oligoarthritis; RF-PA, rheumatoid factor–negative polyarthritis; RF+PA, rheumatoid factor–positive polyarthritis; ERA, enthesitis-related arthritis; PsA, psoriatic arthritis; AO, other arthritis
N/A, not applicable/available.

Active uveitis

Step I: Start of treatment

```

graph TD
    A[Prognostic factors for impending loss of visual acuity:  
poor visual acuity at baseline, hypotension,  
glaucoma, cataract, macular edema,  
dense opacities of vitreous] --> B[Present]
    A --> C[Not present]
    B --> D[Topical corticosteroids  
(prednisolone acetate 1%)  
Dosage: during acute episodes: 1st-3rd  
day every two hours to every hour,  
then reduce according to degree of severity]
    C --> E[Topical corticosteroids  
(prednisolone acetate 1%)  
Dosage: during acute episodes: 1st-3rd  
day every two hours to every hour,  
then reduce according to degree of severity]
    D --> F[+]
    E --> F
    F --> G[Systemic corticosteroids  
(prednisolone)  
Dosage: p. o. initially 1-2 mg/kg body weight,  
p. o. reduce ≤ 0.15 mg/kg body weight over 4 weeks,  
If possible restrict use to a few weeks only.  
Or i. v. pulse with methylprednisolone 20-30 mg/kg body  
weight]
    D --> H[Inactivity]
    E --> I[Inactivity]
    F --> J[Not inactive or reactivated when dose >3 drops or 0.15 mg/kg body weight of prednisolone or  
if new complications arise]
    G --> I
  
```

Step II: After about 12 weeks (or earlier, depending on clinical course)

```

graph TD
    A[Methotrexate  
Dosage: 15 mg/m2 per week, s.c. or p.o.  
(preferred immunosuppressant)] --> B[or]
    C[Azathioprin  
Dosage: 2-3 mg/kg body weight  
p.o.] --> B
    B --> D[Topical corticosteroids  
(prednisolone acetate 1%)  
≤ 3 drops additionally,  
as little as possible, depending on clinical  
course]
    D --> E[Inactivity]
    D --> F[Not inactive or reactivated or if new complications arise]
  
```

Step III: After about 16 weeks (or earlier, depending on clinical course) additionally

```

graph TD
    A[Adalimumab  
Dosage: 24 mg/m2 s.c.  
every 2 weeks  
(preferred TNF-α inhibitor)] --> B[or]
    C[Infliximab  
Dosage: 3-10 mg/kg body weight  
i. v.  
every 4-8 weeks] --> B
    D[Ciclosporin A  
Dosage: initially 3 mg/kg body  
weight p.o.] --> B
    B --> E[Topical corticosteroids  
(prednisolone acetate 1%)  
≤ 3 drops additionally  
as little as possible, depending on clinical  
course]
  
```

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2015; 112: 92–100

BOX 3

Requirements and perspectives for the future

- Definition of better outcome indicators in order to identify at-risk patients early (current study of the Multinational Interdisciplinary Working Group for Uveitis in Childhood)
- Research into biomarkers in order to be able to predict disease manifestations, prognosis, tissue damage, and therapeutic response
- Prompt and timely licensing of standard medications (for example, TNF-alpha inhibitors) for use in JIA-associated uveitis and further effective agents as orphan drugs required
- Putting in place accompanying complex medical treatments to improve the disease course, quality of life, and integration of chronically ill patients into society

course of the uveitis include visual acuity, the number of cells in the anterior chamber as seen on slit-lamp examination, and complications (12, 30). Furthermore, activity, severity, and functional impairments in everyday life as a result of JIA and uveitis need to be assessed by using evaluated measuring instruments (30). Furthermore, patients' global and uveitis-related quality of life needs to be assessed over the disease course (6, 30).

Uncertainties about the best way to proceed persist particularly in the context of stopping immunosuppressant therapies. The risk of recurrence seems reduced by 90% if methotrexate treatment is given for three years or longer, or for an additional minimum of two more years after achieving an inflammation-free status (31). The search is on for reliable biomarkers to assess inflammatory activity in order to reduce the risk of recurrences after stopping treatment with DMARDs. According to initial study data, the myeloid-related proteins (MRP)-8 and MRP-14 are promising candidates in JIA (32, e214). In an initial study in patients with JIA-associated uveitis, the serum concentrations of MRP8/14 correlated independently with the activity of the arthritis and uveitis (e25).

Management of complications threatening visual acuity

Cataract surgery is technically demanding because of the accompanying risk of subsequent harms in the anterior ocular segment (for example, synechiae, opacities of the vitreous). Using a "small incision technique" and ensuring complete perioperative inflammation control in specialist centers can nowadays justify implantation of intraocular lenses in selected patients from school age (IIIB) (33–35, e26).

Glaucoma is often not adequately controlled with the available pressure-lowering medications, hence surgery is required (15, 36). The currently favored method entails filtering interventions with intraoperative topical application of antimetabolites (IIIA) and drainage implants (IIIA).

Macular edema in uveitis requires systematic treatment. According to a recent position statement from the ophthalmological societies in Germany (e27), the ocular inflammation should be treated according to current standards. In case of therapeutic failure when using acetazolamide (IO), parabolbar (IIA) and/or systemic corticosteroids (IIA), intravitreal corticosteroids (IA) or anti-vascular endothelial growth factor (anti-VEGF) (IB) should be administered where necessary (e27).

Prognosis

Compared with intraocular inflammation in adults, the prognosis for visual acuity remains poorer in JIA-associated uveitis (2, 3, 5, 13). One third of children develops unilateral or even bilateral loss of visual acuity. The rate of sight loss in the early 1990s was reported to be 18% of affected eyes; currently, this rate is estimated to be 5% (5). This improvement is attributed to better screening for uveitis and subsequently earlier diagnosis of uveitis. Pediatricians and maybe also general practitioners have a crucial role in preventing sight loss in this setting. Furthermore, the advantages of systematic suppression of the inflammation are obvious (19, e28). In a cohort of patients with JIA-associated uveitis in the multicenter Systemic Immunosuppressive Therapy for Eye Diseases (SITE) study, control of the inflammation and the use of immunosuppressants were significantly associated with a reduced risk for loss of visual acuity (19). It is highly desirable for these effective medications not to be withheld from patients with a severe disease course. If the drugs are used in a guideline-conform manner the statutory health insurers should reimburse the costs. The long term disease course has been proved to be better if a uveitis center is involved from an early stage (2, e14).

In a recent study, JIA patients who received methotrexate treatment early after the onset of their arthritis were affected by uveitis only half as often in their first few years of illness as JIA patients who had not received immunosuppressants (37). Correspondingly, uveitis prophylaxis might constitute a further indication for initial treatment with methotrexate, in addition to the current indications (high activity and poor arthritis prognosis).

In the past the assumption was that the inflammation in the joints and eyes would "burn itself out" during puberty. More recent studies in adults with JIA have, however, shown remission rates of 40–60% (38) for the arthritis and of only 50% for the uveitis. It is a sobering fact that the disease activity of JIA and the uveitis associated with it can persist into adulthood even when modern biological DMARDs are used (40), so that a considerable number of patients require additional treatment in adulthood.

Box 3 lists requirements and perspectives for the future.

KEY MESSAGES

- Uveitis screening by an ophthalmologist has to start immediately after a diagnosis of JIA and in all children in whom JIA is urgently suspected; screening should be continued at appropriate intervals.
- The aim of therapeutic management is the complete absence of inflammation; to achieve this, DMARDs will have to be administered in many cases.
- The high rates of uveitis and its high complication rates underline the need for interdisciplinary care in centers with special expertise in the areas of uveitis and pediatric rheumatology.
- In order to optimize the treatment of JIA-associated uveitis, prospective clinical studies are urgently needed.
- More intensive basic research is majorly important in order to identify innovative approaches to diagnostic evaluation and treatment.

Conflict of interest statement

Professor Heiligenhaus has received study funding (third party funding) from Pfizer and Novartis and has received honoraria for conducting studies from AbbVie, Alimera Sciences, Allergan, MSD, Santen, and Xoma.

Dr Minden has received consultancy fees (advisory board) from Abbvie, Pfizer, Novartis, and Roche/Chugai. She has received speaker honoraria from Pfizer, Abbvie, Roche/Chugai, Medac, and Pharm-Allergan and honoraria for conducting studies from Novartis, Centocor, Abbvie, Pfizer, BMS, and Roche. She has received study funding (third party funding) from Abbvie and Pfizer.

Professor Föll has received consultancy fees from Pfizer, Novartis, Chugai, and Swedish Orphan Biovitra. He has been reimbursed conference participation fees and travel expenses as well as consultancy fees from Pfizer and Novartis.

Professor Pleyer is principal investigator, speaker or consultant on behalf of Abbott, Alcon, Allergan, Amgen, Bausch and Lomb, Bayer/Schering, Centocor, Esba Tech, Essex Pharma, Novartis, Thea, Ursapharm, and Winzer. He has received speaker honoraria from Abbott, Allergan, Centocor, Pfizer, and Novartis.

Manuscript received on 18 June 2014, revised version accepted on 30 October 2014.

Translated from the original German by Birte Twisselmann, PhD.

REFERENCES

1. Paivonsalo-Hietanen T, Tuominen J, Saari KM: Uveitis in children: population-based study in Finland. *Acta Ophthalmol Scand* 2000; 78: 84–8.
2. Edelsten C, Reddy A, Stanford MR, Graham EM: Visual loss associated with paediatric uveitis in english primary and referral centers. *Am J Ophthalmol* 2003; 135: 676–80.
3. Heiligenhaus A, Heinz C, Edelsten C, Kotaniemi K, Minden K: Review of the year: epidemiology of juvenile idiopathic arthritis and its associated uveitis: the probable risk factors. *Ocul Immunol Inflamm* 2013; 21: 180–91.
4. Petty RE, Southwood TR, Manners P: International league of associations for rheumatology. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390–2.
5. Carvounis PE, Herman DC, Cha S, Burke JP: Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. *Graefes Arch Clin Exp Ophthalmol* 2006; 244: 281–90.
6. Angeles-Han ST, Griffin KW, Harrison MJ, et al.: Development of a vision-related quality of life instrument for children ages 8–18 years for use in juvenile idiopathic arthritis-associated uveitis. *Arthritis Care Res* 2011; 63: 1254–61.
7. Minden K, Niewerth M, Listing J, et al.: The economic burden of juvenile idiopathic arthritis-results from the German paediatric rheumatologic database. *Clin Exp Rheumatol* 2009; 27: 863–9.
8. Berntson L, Andersson Gare B, Fasth A, et al.: Nordic Study Group Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. *J Rheumatol* 2003; 30: 2275–82.
9. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K: Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology* 2007; 46: 1015–9.
10. Kotaniemi K, Kautiainen H, Karma A, Aho K: Occurrence of uveitis in recently diagnosed juvenile chronic arthritis. A prospective study. *Ophthalmology* 2001; 108: 2071–5.
11. Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM: An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol* 2002; 86: 51–6.
12. Jabs DA, Nussenblatt RB, Rosenbaum JT, et al.: Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol* 2005; 140: 509–16.
13. Thorne JE, Woreta F, Kedhar SR, Dunn JP, Jabs DA: Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. *Am J Ophthalmol* 2007; 143: 840–6.
14. Sijssens KM, Rothova A, Berendschot TTJM, de Boer JH: Ocular hypertension and secondary glaucoma in children with uveitis. *Ophthalmology* 2006; 113: 853–9.
15. Heinz C, Koch JM, Zurek-Imhoff B, Heiligenhaus A: Prevalence of uveitic glaucoma and success of non-surgical treatment in adults and children in a tertiary referral center. *Ocul Immunol Inflamm* 2009; 17: 443–8.
16. De Boer J, Steljaert A, van den Bor R, Stellato R, Osseward-van Norel J: Development of macular edema and impact on visual acuity in uveitis associated with juvenile idiopathic arthritis. *Ocul Immunol Inflamm* 2014; (Epub ahead of print).
17. Kanski JJ: Anterior uveitis in juvenile rheumatoid arthritis. *Arch Ophthalmol* 1977; 95: 1794–7.
18. Bolt JB, Cannizzaro E, Seger R, Saurenmann RK: Risk factors and long-term outcome of juvenile idiopathic arthritis-associated uveitis in Switzerland. *J Rheumatol* 2008; 35: 703–6.
19. Gregory II AC, Kempen JH, Daniel E, et al: Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: The SITE study. *Ophthalmology* 2013; 120: 186–92.
20. De Boer J, Wulffraat N, Rothova A: Visual loss in uveitis of childhood. *Br J Ophthalmol* 2003; 87: 879–84.
21. Chia A, Lee V, Graham EM, Edelsten C: Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. *Am J Ophthalmol* 2003; 35: 757–62.
22. Woreta F, Thorne JE, Jabs DA, Kedhar SR, Dunn JP: Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis (JIA). *Am J Ophthalmol* 2007; 143: 647–55.
23. Braakenburg AM, de Valk HW, de Boer J, Rothova A: Human leukocyte antigen-B27-associated uveitis: long-term follow-up and gender differences. *Am J Ophthalmol* 2008; 145: 472–9.
24. Heiligenhaus A, Michels H, Schumacher C, et al.: Evidence-based, interdisciplinary guidelines for anti-inflammatory

- treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int* 2012; 32: 1121–33.
25. Lovell DJ, Ruperto N, Goodman S, et al.: Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008; 359: 810–20.
  26. Zannin ME, Birolo C, Gerloni V, et al.: Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. *J Rheumatol* 2013; 40: 74–9.
  27. Heiligenhaus A, Miserocchi E, Heinz C, Gerloni V, Kotaniemi K: Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). *Rheumatology* 2011; 50: 1390–4.
  28. Tappeiner C, Heinz C, Ganser G, Heiligenhaus A: Is tocilizumab an effective option for treatment of refractory uveitis associated with juvenile idiopathic arthritis? *J Rheumatol* 2012; 39: 1294–5.
  29. Zulian F, Balzarini M, Falcini F, et al.: Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis. *Arthritis Care Res* 2010; 62: 821–5.
  30. Heiligenhaus A, Foeldvari I, Edelsten C, et al.: Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multi-national interdisciplinary working group for uveitis in childhood. *Arthritis Care Res* 2012; 64: 1365–72.
  31. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH: Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol* 2011; 151: 217–22.
  32. Foell D, Wulffraat N, Wedderburn LR, et al.: Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. *JAMA* 2010; 303: 1266–73.
  33. Kotaniemi K, Penttilä H: Intraocular lens implantation in patients with juvenile idiopathic arthritis-associated uveitis. *Ophthalmic Res* 2006; 38: 318–23.
  34. Sijssens KM, Los LI, Rothova A, et al.: Long-term ocular complications in aphakic versus pseudophakic eyes of children with juvenile idiopathic arthritis-associated uveitis. *Br J Ophthalmol* 2010; 94: 1145–9.
  35. Häberle H, Velhagen KH, Pleyer U: Pseudophakie bei Kindern mit juveniler Arthritis. *Ophthalmologe*. 1998; 95: 823–7.
  36. Foster CS, Havlikova K, Baltatzis S, Christen WG, Merayo-Llves J: Secondary glaucoma in patients with juvenile rheumatoid arthritis-associated iridocyclitis. *Acta Ophthalmol Scand* 2000; 78: 576–9.
  37. Papadopoulou C, Kostik M, Böhm M, et al.: Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. *J Pediatr* 2013; 163: 879–84.
  38. Ravelli A: Toward an understanding of the long-term outcome of juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2004; 22: 271–5.
  39. Kotaniemi K, Arkela-Kautiainen M, Haapasaari J, Leirisalo-Repo M: Uveitis in young adults with juvenile idiopathic arthritis: a clinical evaluation of 123 patients. *Ann Rheum Dis* 2005; 64: 871–4.
  40. Vidqvist KL, Malin M, Varjolahti-Lehtinen T, Korpela MM: Disease activity of idiopathic juvenile arthritis continues through adolescence despite the use of biologic therapies. *Rheumatology* 2013; 52: 1999–2003.

Corresponding author:

Prof. Dr. med. Arnd Heiligenhaus
Augenabteilung am St. Franziskus Hospital
Hohenzollernring 74
48145 Münster
arnd.heiligenhaus@uveitis-zentrum.de

For eReferences please refer to:
www.aerzteblatt-international.de/ref0615

eTables:
www.aerzteblatt-international.de/15m0092

REVIEW ARTICLE

Uveitis in Juvenile Idiopathic Arthritis

Arnd Heiligenhaus, Kirsten Minden, Dirk Föll, Uwe Pleyer

eREFERENCES

- e1. Kotaniemi K, Kaipainen-Seppanen O, Savolainen A, Karma A: A population-based study on uveitis in juvenile rheumatoid arthritis. *Clin Exp Rheumatol* 1999; 17: 119–22.
- e2. Hudde T, Neudorf U, Heiligenhaus A, et al.: Diagnostik bei Uveitis im Kindesalter: Welche Tests bei welcher Uveitis? *Klin Monatsbl Augenheilkd* 2007; 224: 494–9.
- e3. Schüler A, Coupland SE, Krause L, Bornfeld N: Maligne und nicht-maligne Uveitis-Maskierungssyndrome im Kindesalter. *Klin Monatsbl Augenheilkd* 2007; 224: 477–82.
- e4. Dreesbach J, Zurek-Imhoff B, Böttner K, Mussinghoff P, Heinz C, Heiligenhaus A: Krankheitskosten bei juveniler idiopathischer Arthritis-assoziiierter Uveitis. *Der Ophthalmologe* 2013; 110: 29.
- e5. Modesto C, Antón J, Rodríguez B, et al.: Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). *Scand J Rheumatol* 2010; 39: 472–9.
- e6. Watanabe Duffy KN, Lee J, Guzman J, et al.: The research in arthritis in Canadian children emphasizing outcomes (ReACCh Out) cohort. Prospective determination of the incidence of new onset uveitis in juvenile idiopathic arthritis. *Arthritis Rheumatol* 2014; 66 (Suppl 11): S21–2.
- e7. Zeggini E, Packham J, Donn R, et al.: Association of HLA-DRB1*13 with susceptibility to uveitis in juvenile idiopathic arthritis in two independent data sets. *Rheumatology* 2006; 45: 972–9.
- e8. Angeles-Han ST, McCracken C, Pichavant M, et al.: HLA associations in a matched cohort of juvenile idiopathic arthritis children with and without uveitis. *Arthritis Rheumatol*. 2014; 66: 160–1.
- e9. Saurenmann RK, Rose JB, Tyrrell P, et al.: Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort. Ethnicity as a risk factor. *Arthritis Rheum* 2007; 56: 1974–84.
- e10. Linssen A, Rothova A, Valkenburg HA, et al.: The lifetime cumulative incidence of acute anterior uveitis in a normal population and its relation to ankylosing spondylitis and histocompatibility antigen HLA-B27. *Invest Ophthalmol Vis Sci* 1991; 32: 2568–78.
- e11. Ducos de Lahitte G, Terrada C, et al.: Maculopathy in uveitis of juvenile idiopathic arthritis: an optical coherence tomography study. *Br J Ophthalmol* 2008; 92: 64–9.
- e12. Wolf MD, Lichter PR, Ragsdale CG: Prognostic factors in the uveitis of juvenile rheumatoid arthritis. *Ophthalmology* 1987; 94: 1242–8.
- e13. Chalom EC, Goldsmith DP, Koehler MA: Prevalence and outcome of uveitis in a regional cohort of patients with juvenile rheumatoid arthritis. *J Rheumatol* 1997; 24: 2031–4.
- e14. Dana MR, Merayo-Llloves J, Schamberg DA, Foster CS: Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. *Ophthalmology* 1997; 104: 236–44.
- e15. Zulian F, Martini G, Falcini F, et al.: Early predictors of severe course of uveitis in oligoarticular juvenile idiopathic arthritis. *J Rheumatol* 2002; 29: 2446–53.
- e16. Kalinina Ayuso V, Makhotkina N, van Tent-Hoeve M, et al.: Pathogenesis of juvenile idiopathic arthritis associated uveitis: the known and unknown. *Surv Ophthalmol* 2014; 59: 517–31.
- e17. Foeldvari I, Wierk A: Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005; 32: 362–5.
- e18. Heiligenhaus A, Mingels A, Heinz C, Ganser G: Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. *Eur J Ophthalmol* 2007; 17: 743–8.
- e19. Biester S, Deuter C, Michels H, et al.: Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007; 91: 319–24.
- e20. Simonini G, Taddio A, Cattalini M, et al.: Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab and infliximab. *Arthritis Care Res* 2011; 63: 612–8.
- e21. Smith JA, Thompson DJ, Whitcup SM, et al.: A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 53: 18–23.
- e22. Tappeiner C, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A: Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. *Eye* 2009; 23: 1192–8.
- e23. Bratton ML, He YG, Weakley DR: Dexamethasone intravitreal implant (Ozurdex) for the treatment of pediatric uveitis. *J AAPOS* 2014; 18: 110–3.
- e24. Gerss J, Roth J, Holzinger D, et al.: Phagocyte-specific S100 proteins and high-sensitivity C reactive protein as biomarkers for a risk-adapted treatment to maintain remission in juvenile idiopathic arthritis: a comparative study. *Ann Rheum Dis* 2012; 71: 1991–7.
- e25. Walscheid K, Holzinger D, Heinz C, et al.: S100 A8/A9 serum levels are elevated in juvenile idiopathic arthritis-associated uveitis. *Pediatric Rheumatol* 2013; 11: 80.
- e26. Grajewski RS, Zurek-Imhoff B, Roesel M, Heinz C, Heiligenhaus A: Favorable outcome after cataract surgery with IOL implantation in uveitis associated with juvenile idiopathic arthritis. *Acta Ophthalmol* 2012; 90: 657–62.
- e27. Heiligenhaus A, Bertram B, Heinz C, et al.: Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands zur intravitrealen Therapie des Makulaödems bei Uveitis. *Der Ophthalmologe* 2014; 111: 740–8.
- e28. Schenck S, Klotsche J, Niewerth M, et al.: Inzidenzanalyse der JIA – assoziierten Uveitis im zeitlichen Verlauf (2000–2012). *Monatsschr Kinderheilkd* 2014; 162: 252.

eTABLE 1

Classification of the evidence

Level	Evidence
I	> 1 randomized controlled trial (RCT) of good quality
II	Individual RCTs, >1 controlled, but non-randomized trial or >1 RCT of lesser quality
II	Cohort or case-control studies preferably from more than one research group or more than one center Observations of very clear effects within non-controlled studies
III	Expert opinion, clinical experience, or descriptive studies, cohort studies or case-control studies, studies of inferior quality

eTABLE 2

Classification of recommendations

Strength	Recommendation
A	Strongly recommended
B	Recommended
0	Open